

# Extrapolation of Carcinogenic Risk from Animal Experiments to Man

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When estimating the absolute risk of cancer, the shape of the dose-response curve in the region of doses where actual exposure of man occurs is of crucial importance. This shape is equally important for the determination of relative risks, as in the comparison of risks from alternative energy sources. Experimental and epidemiologic studies are, for various reasons, unable to give sufficiently exact information concerning the dose response in the low dose region. Therefore, the discussion concerning dose-response relationships also has to consider biologically reasonable mechanisms for the origin of tumors.

## Mutation Hypothesis

Although it is realized that the development of cancer is a two-step or multistep process, the current hypothesis concerning the origin of cancer assumes that one or a few mutational events are involved in the initiation of tumors (1). This hypothesis is supported not only by the strong, qualitative correlation between mutagenic and carcinogenic activities of chemicals but also by certain reaction-kinetic considerations, viz., a favoring of both the carcinogenic and the mutagenic potential by a relatively high reactivity towards certain centers in DNA such as guanine-O<sup>6</sup> (2). In one case, the role in cancer initiation of a well-defined chemical change in the DNA, the ultraviolet-induced thymine dimer, has further been described (3).

## Linearity of Dose Response at Low Doses

A number of experiments in microorganisms, plants, and animals give strong evidence that frequencies of mutants observed in offspring generations after exposure to ionizing radiation or mutagenic chemicals, depend linearly on dose in the low-dose region (4). [Here "dose" refers to the tissue dose  $D_t$  defined as the time integral of the con-

centration in the target cells of the proximal mutagen/carcinogen (5). Under certain conditions,  $D_t$  is proportional to the exposure dose  $D_e$ .] If a mutation process, comprising  $m$  mutational events in each of  $n$  cells, were rate-limiting in the origin of tumors, a target-theoretical representation (6) of the fraction of individuals with tumors,  $N^*/N_0$ , gives

$$N^*/N_0 = (1 - e^{-kD})^{mn}$$

where  $D$  is dose and  $k$  is a proportionality constant. A diagrammatic presentation in semilogarithmic scale of the fraction of animals without tumors,  $\log(1 - N^*/N_0) = \log N/N_0$ , as a function of dose  $D$  then approaches a straight line with the intercept  $\log mn$  at  $D = 0$ , permitting an estimate of the number of targets  $mn$ . Such representation of experimental data from studies of both primary and secondary carcinogens gives straight lines extrapolating to  $\log 1$ , i.e.,  $mn = 1$ . With some care required because of a possible sensitivity variation of cells, which may lead to a decrease of the extrapolation number (6), the conclusion would be that in these cases a limiting step in the origin of tumors consists in one mutational event in one cell, and further that the dose-response curve is linear from dose zero onwards. It should be kept in mind that if the dose-response curve contains higher-order terms of the dose, great care is required in the decision, on the basis of experimental data, whether a linear component exists at low doses, as well as in the determination of its slope (7).

The involvement of one cell only is in agreement with other observations in favor of a monoclonal

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origin of many tumors (8). In the past, a linear dose response in the low-dose region, of chemically and radiation-induced cancer has been questioned, on the basis of arguments which, in no case, are tenable (4). For instance, the biochemical repair of DNA damage is sometimes put forward as one factor contributing to a no-effect level below a safe threshold dose (9). However, why should the DNA repair be 100% effective for mutational events leading to cancer transformation when it is not for other types of mutation? As a matter of fact, no proofs exist against a linear dose response in studied cases (and, therefore, of overall carcinogenicity of the agents in question), and most indications of a safe dose threshold may be explained as artifacts caused by too small a sample size. In animal samples of limited size, terms of higher order of the dose-response curve will often predominate, partly as functions of a cocarcinogenic or promoting action of "complete" carcinogens, disturbances of the repair systems, or enzyme induction, i.e., effects expected to require that a certain minimum dose is exceeded.

## Extrapolation from Animals to Man

Extrapolation of data from acute toxic effects is generally done from laboratory animals to human exposures in quantitative terms, for instance, in order to estimate safe levels of human exposures. This is done with the assumption that physiological parameters in animals and humans are comparable (10). The calculation often involves the use of safety factors. Few data are available for comparisons of late effects (11). The mechanism of tumor induction is probably the same for humans and animals, although the risk, for e.g., for the mouse, may differ from the human risk due to differences in uptake, biotransformation, distribution, and elimination, i.e., in factors that determine actual tissue doses.

The animal experiment is a rather crude instrument for detecting carcinogenic activity. An experiment dealing with 59 animals in each dose group cannot detect a carcinogenic risk under 5% (12), a risk level probably unacceptable in the human situation. Only by increasing the number of animals to thousands and hundreds of thousands, can low risk levels thus be defined. This statement presupposes that the control animals in the experimental system will not show up with spontaneous tumors. Should this be the case, the sensitivity of the conventional test system is much further decreased (13). This fact is an argument against extrapolating dose data

from conventional animal test systems to the human exposure situation, particularly as far as large human populations are concerned.

The fractionation of single doses of carcinogens, i.e., the administration of the same total dose over a long time period, seems to increase the response to polycyclic hydrocarbons (14). Should this be a characteristic of other carcinogens, it would mean that the exposure to low doses over a long time could be more effective than a short high-dose exposure.

An inverted relationship between dose and latency time has frequently been observed (15): a low dose gives a long mean latency time and a high dose a short mean latency time, although not proportionally so (16). This has been taken as an indication that it could, at least theoretically, be possible to extrapolate to such a low dose that the mean latency time exceeds the expected lifetime of the species studies. Such a calculation does, however, not take into account the fact that the variation in latency time increases with decreasing dose. A small dose may thus give individual latency times within the expected lifetime although the mean latency time for the group as a whole exceeds the life span.

In the specific case of lung cancer, further arguments against attempts to extrapolate experimental dose data of carcinogens to so called no-effect levels, or "safe" levels of human exposure, are that administration by inhalation is seldom used or is not particularly effective in producing cancer in small laboratory animals. The use of peroral administration or other routes of administration different from the route of administration characteristic of the human exposure makes quantitative extrapolation even more difficult. Laboratory animals are furthermore usually genetically well characterized, they are exposed to one carcinogenic chemical in their lifetime, the experiment is started at a similar age and body weight, and other environmental conditions are controlled for all individuals in the test population. For human populations none of these "ideal" conditions is present. The great variation in biological sensitivity in human populations, for instance, introduces an important drawback to a quantitative extrapolation of experimental dose data.

This is not to say that experimental dose-response studies are useless. In fact, their most important contribution to the control of human exposure to carcinogens lies in the applicability of the mathematical models to epidemiologic data under the aforementioned assumptions that the mechanism of cancer induction and the toxicological parameters of carcinogenic chemicals are the same in humans

and animals. When applying such a model to epidemiological data it should, however, be remembered that a deviation from the linear dose-response relationship, with a higher effectiveness of lower doses, may occur at least for certain cancers as observed for radiation (17), urethane (18), and vinyl chloride (19, 20).

When considering extrapolation of risk to man of a factor added to his environment it is of further importance that human populations live under a constant pressure of cancer-initiating as well as cancer-promoting events. It was recently shown (21) that, irrespective of the mathematical model applied, any carcinogen added to this complicated environment will cause an increment in the total cancer incidence from dose zero onwards (of the particular carcinogen considered). This conclusion is valid for tumors with a monoclonal origin (8).

Methods to measure tissue doses  $D_t$  for primary and secondary mutagens/carcinogens have been suggested (5, 22). Furthermore, the risk of mutation relative to the corresponding risk for ionizing radiation could be shown to follow a simple function of the dose, which, since it was found to be valid for so widely differing organisms as bacteria, plants and rodents, would at least preliminarily apply also to man. Certain indications are at hand that the same expression is valid also for induced cancer (23). If further work can confirm that this is the case, and since dose measurements can be applied directly to exposed persons, a way would be at hand to overcome many of the difficulties in estimating the human risk.

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